Emerging from the dark side: new therapeutic applications of scheduled psychoactive substances

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The discovery and development of new medicines occupies years of painstaking and expensive scientific work, with multidisciplinary teams working together in the hope of developing a new chemical entity that outperforms the current standard of care within the chosen disease setting. Once optimised in the laboratory and achieving acceptable regulatory pre-clinical benchmarks, years of clinical evaluation are required to persuade the regulatory authorities of a new agent's superior efficacy in order to license a new medicine. In short, drug discovery is a high-risk and expensive business [1], with most drug candidates failing (ideally early) along the development pathway and the full cost of new drug development from 'bench to bedside' averaging out at an estimated $2.6 billion [2]. On the other hand, the rewards available to those companies with the global reach and resources to launch a new drug are considerable. Drug market dynamics partly explain why new branded products tend to be expensive (pitched at a price that the market can sustain), with market exclusivity protected by patent filings. It also partly explains why there is relatively little progress in areas of unmet medical need where patients and their healthcare systems simply cannot afford to pay high prices for new medicines, such as certain tropical infectious diseases.

Despite the perverse incentives towards chronic disease with large market potential, new medicine discovery as outlined above is generally regarded as the acceptable face of drug development.

In a previous editorial [3] we outlined the development of new psychoactive substances, often seen as the dark side or unacceptable face of medicinal chemistry and drug discovery. Within this market, there is little scientific rigour, and no painstaking attention to pharmaceutical quality control, or indeed toxicity testing to protect the welfare of the consumer [4]. On the other hand, it is notable that amongst the bewildering array of new psychoactive substances consumed, many are analogues or close relatives of compounds originally discovered within pharmaceutical industry laboratories for potential treatment of CNS disorders.

In this perspective, we highlight the emergence of two drugs (Figure 1) with a bad reputation – MDMA (ecstasy) and the prodrug psilocybin (from psilocybe mushrooms) – in the effective treatment of psychological disorders and their possible future availability within a healthcare context. These two selected examples, snapshots of growing activity in this field, serve to highlight the often-cited need for a grown-up and informed debate around use of scheduled (controlled) drugs.

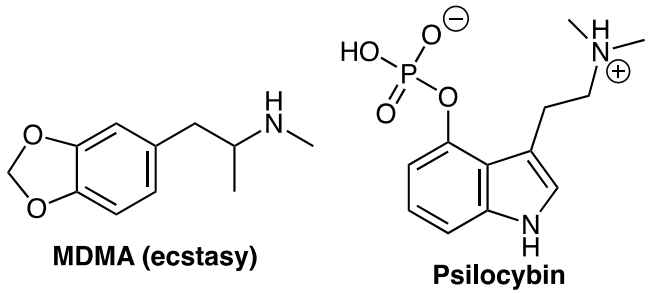

Figure 1. Chemical structures of MDMA (ecstasy) and psilocybin.

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy; Molly) is a stimulant psychoactive drug commonly used in a recreational setting [4,5]. In most countries MDMA is illegal as a consequence of its stimulant, empathogenic and entactogenic properties, popularity as a party drug, and occasional reported fatal overdose. The unregulated market around this illegal drug means that MDMA is sold in varying doses and often adulterated with other substances such as ephedrine and paramethoxyamphetamine [4]. Remarkably it was estimated that around 22 million people worldwide used ecstasy in 2015, according to the UN World Drug Report [101]. Due to the numbers of users of MDMA worldwide, and comparative safety of pharmaceutical quality MDMA at low doses, there may be a future for MDMA to be sold in a healthcare setting for reducing the

harms caused by recreational drugs such as black market ecstasy and new psychoactive substances [6].

MDMA has a range of effects including modulation of the serotonergic and noradrenergic systems; and induces release of the social bonding hormone oxytocin by binding to 5-HT_{1A} receptors on hypothalamic oxytocin-containing neurons. [7,8]. The effects of increased openness and empathy are reported as being a major component of the therapeutic effect of MDMA in psychotherapy and its continued recreational use [9].

MDMA has been used as an adjunct to psychotherapy since the 1970s, when it was used as an alternative to MDA in psychotherapy sessions after MDA was made illegal in 1970 [10]. The synthesis and studies into the psychoactive effects of MDMA were conducted by Alexander Shulgin and his wife Ann Shulgin who conducted further research into MDMA's potential uses in psychotherapy [10]. MDMA started to be used by psychotherapists as an effective aid to treatment until the drug's scheduling by the US Drug Enforcement Agency pushed MDMA-assisted psychotherapy underground in the 1980s. Recently, phase III clinical trials into MDMA-assisted psychotherapy have been approved after successful completion of phase II studies for ex-military personnel, firefighters and police officers with post-traumatic stress disorder [11].

The chemical structure of psilocybin (Figure 1) is related to serotonin. Extensive research has suggested that after psilocybin has been metabolised (via dephosphorylation) to the pharmacologically active molecule psilocin, it mediates effects on the G protein-coupled 5-HT_{2A} serotonin receptors [12,13]. Agonism of 5-HT_{2A} receptors has effects on neuroplasticity, environmental sensitivity, learning and psychological adaptability [8].

Psilocybin has been studied for a range of conditions including alcohol [14] and tobacco [15] addiction, depression [16] and existential anxiety associated with life-threatening illness [17]. Recent studies have suggested that the mystical-type experience sometimes associated with psilocybin experiences has been correlated with therapeutic effects and a long-term increase in openness [17]. The results of these recent studies show psilocybin can, through the mystical experience, promote enduring changes in personality traits, priorities/values and improve emotional regulation. These observations suggest that psilocybin-assisted psychotherapy could have a positive effect on a societal level and may ultimately become an important component of mainstream Western medicine.

Lesser known, potentially beneficial applications of psilocybin could be described as being in the field of positive psychology. The current medical paradigm consists of attempting to bring

individuals from a poor state of mental health to acceptable or good mental health. There is little provision for attempting to change a person's mental outlook from the baseline state to excellent. Psychotherapeutic interventions typically only take place once a person has become mentally ill. We propose that psilocybin could be used as a preventative therapy in order to decrease the likelihood of at risk individuals developing poor mental health and to increase positive mental outlook. Usage of psilocybin has been associated with reduced likelihood of engaging in antisocial criminal behaviours [18], an enhanced appreciation for nature [19,20] and a decrease in sympathy for politically authoritarian perspectives [20]. In light of the benevolent changes in personality that can arise from the usage of psilocybin, it could be argued that responsible usage of psilocybin in therapeutic settings based on rigorous scientific evidence could assist in socio-environmental challenges such as climate change and interpersonal violence.

It has been shown that, when members of the public are presented with contemporary information on relative harm and potential therapeutic applications, there is public support for these substances to be available in a healthcare setting particularly amongst the university-educated section of the population [6]. Public and mainstream scientific perceptions of these substances are shifting and it is not difficult to envision a future in which MDMA and psilocybin play a role in contemporary medicine.

One important consequence of the prevailing trend towards making psychoactive substances illegal in many countries is that research into the potential therapeutic benefits of these substances is severely curtailed. It has long been known that banning substances does not stop or even reduce psychoactive drug consumption [3]. In the internet age, and with the advent of the dark web, substance prohibition simply changes the nature of the supply chains, driving illicit production of more potent and harmful substances to the detriment of the consumer's mental and physical health. For example, the 2016 U.K. Psychoactive Substances Bill [102] exemplifies the consequences of government policy being driven by mainstream media opinion rather than evidence-based science. The recent unintended rise of potent and harmful synthetic cannabinoids such as 'Spice', particularly amongst the most vulnerable populations, provides one example amongst many of the consequences of ill-informed and reactionary policy making in the U.K. Meanwhile tobacco [103] and alcohol [104] consumption continue unabated in many countries, despite being responsible for more morbidity and mortality than all other illicit products combined [6].

We repeat our previous call [3] for an evidence-based, scientifically informed debate around psychoactive substances, especially where there is evidence for positive benefit to treat rising incidence of mental health and CNS disorders. A vast array of psychoactive substances exist, with potential positive and negative effects for the consumer. Without the ability to carry out rigorous and objective research unimpeded, we will surely miss the opportunity to use psychoactive substances for the benefit of patients suffering from a whole range of disorders.

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